CARCINOMA OF THE PROSTATE*

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WHEN Engelbach in 1888 collected 114 reported cases of malignant tumors of the prostate he did much to clarify the problem of obstruction of the bladder outlet. Even so, it was not before almost a quarter of a century had passed before clear cut differential diagnoses were generally made between benign and malignant prostatic diseases. Even though significant progress was being made, how primitive such a period now appears. Although our successors, principally because of greater knowledge of the steroid hormones, will be in a position to pity our floundering efforts to solve the problem, it is a fact that during the life of every experienced urologist now practicing, prostatic cancers and their proper treatment have become exceedingly important.

These tumors are not rare. It is recognized that of every 100 men who reach the age of sixty years, five will develop prostate cancers. In addition, careful microscopic studies of large numbers of prostates removed because of benign hyperplasia have shown unsuspected nests of cancer cells in approximately 20 per cent. Many ingenious methods of treating these tumors have been devised and skillfully performed; radical operations have been perfected by which not only the entire gland and its capsule but also the seminal vesicles and bladder trigone may be removed; radon and radium implants have been inserted in and about the tumor through the intact perineum, through the perineum with the tumor exposed and suprapubically through the opened bladder; roentgen therapy has been delivered by increasingly powerful units, but in spite of all efforts a cure was rarely achieved.

Surgery failed principally because prostatic cancers grow for a long time without causing any symptoms. When the tumor begins to obstruct the bladder and local symptoms insidiously develop, the disease, with few exceptions, has extended beyond reach of the most radical

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operation. Interstitial radiation, while sufficiently powerful to destroy the tumor in areas closely adjacent to the embedded seeds or needles, failed because of technical difficulties in placing the implants accurately throughout the entire growth. External radiation was unsuccessful because of the radioresistance of adenocarcinomas, the considerable distances of the prostate from the nearest body surfaces and the limitations placed on the method through fear of injuring the bladder or rectum. To illustrate the poor results produced by these methods even when carefully conducted, and to establish a basis of comparison with the results obtained by newer therapy, the statistics of the University of Michigan Hospital are of great interest.

TABLE I

From University of Michigan Hospital

END RESULTS OF 795 CASES OF PROSTATIC CANCER TREATED FROM 1925 TO 1940

Number of patients followed	783
Patients known to be dead	737
Patients now living	46

Nesbit and his associates[1] studied the end results of 795 cases of prostatic carcinoma treated between the years 1925 and 1940 inclusive. They were able to follow accurately 98.5 per cent of all the patients in the group. As shown in Tables I and II, of the 795 men, 737 have died, 605 of prostatic cancers, sixty following operations, and sixty-seven of other known causes. Five patients died of unknown causes.

TABLE II

From University of Michigan Hospital

CAUSE OF DEATH OF 783 PATIENTS WITH PROSTATIC CANCERS BEFORE ENDOCRINE THERAPY

Cancer of prostate	605
Operations	60
Other known causes	67
Unknown causes	5

Although 132 patients did not die primarily of prostatic cancers there is no reason to doubt but that they died with prostatic cancers and would have succumbed to this disease had no intercurrent illness supervened.

Against such a background of well deserved pessimism the announcement of Huggins[2] in 1941 was startling indeed. This investigator reported that men with advanced prostatic cancers could be benefited greatly by the simple operation of castration. Huggins' clinical work was based on a long series of ingenious animal experiments.[3] Dogs' prostates were isolated from their bladders and a study was made of the normal excretion of prostatic fluid. It was then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown also that the administration of estrogens promptly stopped the production of prostatic fluid. It was learned that the administration of androgens caused hyperplasia of the epithelial cells of the prostate and that, in some cases, metaplasia became so pronounced that the appearance of the gland simulated cancer. When estrogens were given, these glands promptly returned to normal. Huggins also showed that after surgical castration prostate secretion stopped and metaplasia of the epithelial cells regressed. Although this work was by far the most complete and authoritative on the hormonal relationships of the prostate, earlier investigators had made a number of interesting observations.

Harvey observed that when the hedgehog hibernates the testes atrophy and the prostate also becomes smaller. He observed also that the prostates of bulls became smaller after castration. In 1893, White,[4] on the basis of animal experiments, stated that the castration of dogs "was followed invariably and promptly by atrophy, first of glandular and then of muscular elements, of the prostate." Two years later the same clinician[5] reported generally favorable results in a group of 111 patients castrated by him and others because of prostatic enlargement. In 1898, results were reported following the castration of a number of women for cancers of the breast. Although this treatment of breast cancer never proved successful, it did stimulate further the treatment of prostatic tumors by modification of the endocrines.

After a few years the treatment of prostatic enlargement by castration was largely abandoned. This was probably due to a number of factors. The majority of patients who visited physicians because of

bladder obstruction perhaps required relief more promptly than could be brought about by the removal of the testes; careful pathological differentiation between benign and malignant enlargements of the gland was not performed routinely; and finally, at this time there was greatly increased interest in the development of surgical methods for the relief of prostatic obstruction. For these reasons and perhaps others it was years before further attempts were made to control prostatic enlargement by endocrine methods. Beginning in 1934, Randall castrated five men who had prostatic cancers. Since it was necessary to relieve obstruction in each of these patients, transurethral resections of the bladder outlet were performed as well. Each of these patients followed a course which appeared to Randall to be what one would expect after transurethral resection alone. Therefore he did not report these operations until 1942. At about the time Randall's work was performed, or shortly later, Munger[6] irradiated the testes of a number of men with prostatic cancers for the purpose of castrating them. He noted that these patients did better than his other patients treated by different methods. A number of competent urologists examined Munger's patients at various intervals after treatment and could palpate no evidence of prostatic carcinoma. Beginning about 1938, a number of investigators began to treat patients with prostatic carcinomas by administering female sex hormones by mouth and by pellets of estrogens inserted beneath the skin.

Another important phase of our subject is the remarkably rapid progress made in chemical laboratories through which tests were perfected to establish detailed diagnoses not only of the nature of the primary tumor but also of the extent of metastases. These tests were concerned principally in measuring the amount of phosphatases in the serum. Phosphatases are enzymes which split organic phosphates to give free phosphate ion. They fall into two groups according to the hydrogen ion concentration, (pH), at which they are most active. The acid phosphatases usually have a broad maximum of activity between pH 4.0 and 5.5, the alkaline phophatases usually are most active in a narrow range between pH 9.0 and 9.5. Their exact properties depend on the tissue of origin and on the substrate used in measuring their activity. In 1935 Kutscher and Wolbergs[7] isolated from the prostate a phosphatase which had its maximal activity in an acid solution. In 1936 the Gutmans and Sproul[8] discovered that bones, the site of metastases from

carcinoma of the prostate, contained acid phosphatase in addition to the usual and well known alkaline bone phosphatase. In 1938 the Gutmans[9] established the fact that there was but little acid phosphatase in the prostates of infants and that this substance increased greatly at puberty when testicular secretion began. These workers found acid phosphatase in the normal adult prostate, the hyperplastic prostate and the cancerous prostate. In 1938 and 1939 the Gutmans and Robinson showed that the acid phosphatase activities of the sera of many patients with metastasizing carcinoma of the prostate were greatly elevated. More recently, Gomori,[10] through his microphosphatase tests, demonstrated that acid phosphatase was present only in the adult epithelial cells of the gland. This was the first exhibition of a secondary sex characteristic of a chemical nature.

Acid phosphatase occurs in many organs, but, with the exception of the prostate gland, no organ ordinarily contains more than one or two Bodansky units per gram of tissue. In the human adult prostate the acid phosphatase activity is high, reaching several hundred units per gram. The production of this enzyme by the prostate apparently requires androgens for its development and therefore does not occur before puberty. The acid phosphatase activity of prostatic carcinoma tissue is usually of the same order of magnitude as that of the normal prostate although it may be less in highly anaplastic carcinomas. Normal human serum contains small amounts of acid phosphatase. This cannot originate in the prostate since the activities of the sera of normal men are the same as those of the sera of normal women who have no organ which contains large amounts of the enzyme. At present the source of acid phosphatase in normal serum is unknown.

Woodard[11] made an important contribution in showing how often elevations in serum acid phosphatase occurred in patients with cancers of the prostate and in those with other diseases. Of seventy-one patients with cancers of the prostate and demonstrable bone metastases 51 or 72 per cent had elevated serum acid phosphatase. Of fifty-six patients with cancers of the prostate and no demonstrable bone metastases 19, or 34 per cent had elevated serum acid phosphatase. No elevations in the serum acid phosphatase have been found in patients with benign hyperplasia of the prostate nor in patients with cancers originating elsewhere which have invaded the prostate. This work and clinical experience appears to show that the acid phosphatase of cancerous

prostatic tissue does not enter the circulation as long as the capsule of the gland is intact. It may enter the circulation and be demonstrable in the serum as soon as local invasion or distant metastasis occurs and it does so somewhat more readily when metastases are in bone than in soft parts. In a few cases (probably not more than 10 per cent) elevations in serum acid phosphatase never occur even in the presence of extensive disseminated disease. In these cases it is possible that the tumor because of its structure produces little acid phosphatase, but additional autopsy material is necessary to prove this hypothesis.

Woodard[12] also assayed the serum of thirty-four women and 167 men who had osteogenic sarcoma, Paget's disease, jaundice of various types, plasma cell myeloma, lymphoma and other diseases not involving the prostate and failed to find any elevations of acid phosphatase. On the basis of this work she concluded that conspicuous elevation in serum acid phosphatase appears to be pathognomonic of metastasizing carcinoma of the prostate.

Many investigators have shown that alkaline phosphatase occurs in the kidney, intestinal mucosa, bones and some other tissues but only that from bones enters the blood stream in significant amounts. This enzyme is excreted by the liver and if this organ is diseased excretion may be impaired and the level in the serum may rise. Alkaline phosphatase production is increased as an essential part of new bone formation and with this activity there is a corresponding increase of the amount in the serum. Metastases to bone from carcinoma of the prostate, being nearly always osteoplastic, cause an increase of serum alkaline phosphatase in about 90 per cent of patients with metastases demonstrable and in some cases before any symptoms referable to bones have occurred. While unlike acid phosphatase, alkaline phosphatase is not specific for carcinoma of the prostate, in a patient without liver disease a rise in serum alkaline phosphatase warrants a strong suspicion that metastases to bones have taken place.

Because of the accuracy of phosphatase assays in showing the clinical status of patients, four reasonably clear cut groups may be recognized on the basis of these tests:

1) Normal men in whom there is no increase in either the serum acid or alkaline phosphatases.

2) Patients with proved cancers of the prostate and normal amounts

of both serum acid and alkaline phosphatases. In this small but important group one may perform radical surgery with a fair chance that the tumor has not grown beyond the gland.

3) A group consisting of the great majority of patients with prostatic carcinoma in whom the tumor has grown through the gland capsule with or without forming demonstrable distant metastases. In our experience the great majority show increased serum acid phophatase.

4) Patients with prostatic cancers which have metastasized to bones. In this group both acid and alkaline phosphatases in the serum are elevated significantly. The amount of alkaline phosphatase in the serum so accurately represents the reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information regarding the immediate status of the patient not obtained by any other examinations such as roentgenograms. When both acid and alkaline phosphatases enter the serum from bone metastases the source of the acid phosphatase is the tumor in the bone while the alkaline phosphatase comes from the bone surrounding the tumor.

The improvement after castration of most patients with apparently hopelessly far advanced prostatic cancers is one of the most spectacular changes to be observed in clinical medicine.[13, 14] The relief of pain from bone metastases probably is most gratifying and it usually occurs within thirty-six hours. Patients bed ridden for months because movements were agonizing and who had, as a result, developed serious contractures of their limbs may begin relearning to walk by the third or fourth postoperative day. Metabolism improves greatly, appetites often become ravenous so that men have doubled their body weight in a few months. Every laboratory test of fitness shows improved health. Improvement not infrequently is of such a degree that these men return to their usual occupations and may even resume activities in sports. Regression in the size of metastases to soft parts is usually prompt. Perhaps the most striking of these is the disappearance of large masses in the lungs, which has been observed many times. The primary tumor also shrinks after castration but at a variable rate and to a variable degree. In some cases one cannot detect any evidence of tumor by rectal palpation a few months after operation but usually regression is not so complete. If the patient had considerable bladder obstruction with correspondingly great quantities of residual urine transurethral resection of the bladder outlet usually is necessary. Roentgenograms of the skele-

ton taken at regular intervals have shown interesting bone changes but as yet we have difficulty in correlating the patient's clinical state with the bone pictures. We have seen patients, apparently much benefited by castration, in whom bone metastases seemed to be spreading. We have also observed what appeared to be improvement in a metastatic area in one side of the pelvis while, at the same time, an obvious metastasis in the other side became visible and grew. However, there is no doubt but that in some cases bone metastases heal, how frequently we do not know.

The testes removed from our patients grossly were normal. Microscopic study showed in practically all cases moderate tubular atrophy with from slight to considerable interstitial cell hyperplasia.

After enjoying greatly improved health for varying periods the men castrated because of advanced metastatic prostatic cancers begin to relapse and die. Usually the onset of relapse is characterized by a return of bone pains.

While observing the effects of castration on about eighty men another group of nearly 100 have been treated with female sex hormones administered by mouth.[15] We have seen no clinical benefit from castration which has not been produced to as great a degree by estrogen therapy although improvement is not so prompt. Relief of pains from bone metastases which occurs so often within twenty-four hours of castration occurs only after estrogens have been given for from ten to fourteen days. The estrogen now used is ethinyl estradiol with the trade name of estinyl. The usual daily dose consists of two tablets, each of .05 milligram, taken on retiring.

Within a month of beginning estrogen therapy feminization of the patient appears. At first the nipples become tender, then the breasts enlarge. Later fat is deposited about the hips, the external genitalia shrink and finally a mons veneris is formed. The skin of the face assumes a finer texture and often the beard thins but it continues to grow. Libido probably is lost to a greater degree with estrogens than after castration, however, few of these patients were active sexually before treatment was started. Psychic changes are few and usually mild. A slight euphoria perhaps is most common. Maniacal states have been described following castration but there probably was instability before operation and a failure on the part of the physician to soothe and encourage the patient and obtain his consent. I have never had a patient

refuse castration and I have never felt compelled to tell him that he had a cancer.

As after castration, patients treated with estrogens often regain their previous physical capacities and carry on comfortably for variable periods when relapse occurs. In our experience there has been little difference in the length of time before relapse after castration or estrogen therapy. We have been able to give no appreciable relief to patients who relapsed after castration by administering stilbestrol, but since estinyl can be given in greater therapeutic quantities, trials with it are now being made although, as yet, they have not proved conclusive. In the same way, our patients who relapsed after estrogens have not been significantly improved by castration. Nesbit, however, reported a patient who failed to benefit from stilbestrol but who was completely relieved by castration. Such an occurrence must be rare.

Thinking it possible that androgen excretion by the adrenals explained relapses I removed both adrenal glands from three men who had relapsed after both castration and treatment with estrogens. None of these men lived more than four days and no further trials were made. Huggins performed the same operation on four patients with little more success.

It will be noted that the foregoing description of the striking response to castration and estrogens applies specifically to patients with advanced cancers of the prostate with bone metastases. Men with less advanced disease without bone metastases and bone pains do not show such prompt or profound benefit. In fact, Herger and Sauer point out that under apparently adequate estrogen therapy metastases develop in this group and they live no longer than patients reported by Bumpus[16] who were in a similar clinical condition and who received no hormonal treatment.

The changes in the serum acid and alkaline phosphatases following modification of the endocrines are of both theoretical interest and clinical importance. When the serum acid phosphatase is elevated before treatment it usually shows a decided drop within a week of castration or within two to three weeks after the beginning of stilbestrol therapy. A more limited experience with estinyl suggests that the effect is similar to that of stilbestrol but further use of this drug may show slight differences. When the serum acid phosphatase is normal before treatment there is no immediate change after either castration or the ad-

ministration of estrogens. When treatment fails to initiate a prompt drop in the serum acid phosphatase the patient usually experiences no clinical improvement. These laboratory data corroborate the clinical observation of Herger and Sauer mentioned above. The presence or absence, therefore, of a prompt response of the serum acid phosphatase to treatment is of great prognostic value.

When a patient who has shown a drop in serum acid phosphatase with clinical improvement later relapses, the onset of clinical relapse, usually indicated by the return of bone pains, may or may not be accompanied by a significant increase in serum acid phosphatase. Sometimes the return of symptoms is preceded by a rise of acid phosphatase. When such a rise occurs it always indicates renewed activity of the disease. Unfortunately, persistence of normal values of serum acid phosphatase does not give assurance that the disease is under control. Probably discrepancies between the clinical onset of relapse and the time relapse is indicated by elevation of serum acid phosphatase are due to the fact that the most clear cut clinical evidence of relapse is the return of bone pains and this symptom may reappear at different stages in the depreciated conditions of different patients. The phosphatase assay, therefore, should be depended on as being the more accurate.

We have employed acid phosphatase assays in another way which has proved of considerable clinical value. Patients are occasionally seen with extensive inoperable tumors which involve the prostate and adjoining portions of the bladder or rectum. In such cases it is important to learn whether the growth originated in the bladder or rectum and invaded the prostate or whether it was primary in the prostate and later invaded the bladder or rectum because in the latter case great benefit may be obtained from endocrine therapy. Since prostatic cancers, even when they infiltrate other organs, contain comparatively large amounts of acid phosphatase, assays of tissue removed from the bladder with a cystoscope or from the rectum with a proctoscope have given a clear cut answer to the problem and have provided a rational basis for successful treatment in a number of cases.

The serum alkaline phosphatase in patients without bone metastases or liver disease is normal. This is not affected by endocrine treatment. As previously stated, the serum alkaline phosphatase is almost always elevated in patients with bone metastases from cancers of the prostate. In our experience within a month after surgical castration 80 per cent

of these men show a significant additional rise of serum alkaline phosphatase to amounts which sometimes become two to three times the initial quantities. When patients continue to have clinical improvement the serum alkaline phosphatase begins to fall after about three months and it may reach normal levels as the bone lesions become quiescent or heal. If clinical improvement is not sustained assays of this phosphatase usually remain high. When stilbestrol is employed only about one-third of the patients show a rise of serum alkaline phosphatase soon after the beginning of treatment. The remaining patients either show no reasonably prompt change when clinical improvement is lacking, or if the clinical response is good there is a gradual decline to normal values. Thus there appears to be a definite biological difference in the reactions of bone metastases to the two types of endocrine treatment.

Some work was done in the laboratories of the Memorial Hospital to show how the endocrines of patients with prostatic cancers were modified by castration or by the administration of stilbestrol. It will be remembered that Huggins[3] believed, as a result of his experimental work with dogs, that the prostatic epithelium, whether normal or cancerous, was dependent for its growth on the relation of estrogenic to androgenic hormones in the blood. Estrogens demonstrably decreased prostatic secretion and androgens increased it in experimental animals. On this basis, therefore, the man with prostatic cancer was castrated for the purpose of removing the source of his androgens. It has been known for several years that men excrete estrogens in their urine. Since they have no ovaries their adrenals have usually been considered the source of these substances. It was thought that castration would not affect the adrenals and that the estrogens, therefore, would remain the same but that there would be a change in the estrogen-androgen relationship toward comparatively higher estrogen and lower androgen values. The administration of estrogens should also cause a similar shift in hormonal relations.

It was surprising to learn that these predicted theoretical changes were not borne out by our laboratory tests. Twenty-seven patients with prostatic cancers were studied in relation to their output of estrogens and androgens before and after castration. Before operation the estrogens averaged 16.6 mouse units per twenty-four hours and the androgens 6.1 milligrams of androsterone equivalent as determined colorimetrically

by the modification of the Zimmerman metadinitrobenzene reaction. Since a healthy young man excretes 15 to 25 milligrams of androgens in a similar period, it will be noted that our patients showed low 17-ketosteroid excretion. After castration, instead of estrogens remaining the same and androgens diminishing, the estrogens dropped in all but one of 16 patients to about one-half (8.5 mouse units) of the pre-castration level while the androgens remained the same or rose slightly (from an average of 6.1 to 7.1 milligrams in the 17 patients tested).

Gonadotropic hormones from the anterior pituitary gland were measured before and after operation in 16 patients. Of these, there was a definite post-castration rise in 11, while 5 showed quantities of this hormone too small to measure. In no case was there a decrease in gonadotropic hormone in the urine after castration.

Quite different from these reactions were those found by assays on 9 men before and after the administration of stilbestrol. Before treatment the estrogens of these men averaged 18.2 mouse units in twenty-four hours, while after treatment the quantity rose tremendously because a certain amount of the stilbestrol was excreted in the urine. The androgens before treatment averaged 8.9 milligrams of androsterone equivalent in twenty-four hours. After treatment these 17-ketosteroids fell in every case to an average of 5.4 milligrams of androsterone equivalent.

Of six patients in whom the excretion rate of gonadotropic hormone was studied before and after the administration of stilbestrol, in none was there a post-treatment rise.

From the viewpoint of hormones excreted in the urine, therefore, the treatment of prostatic cancer by castration differs greatly from treatment with stilbestrol. Castration seems to cut estrogenic excretion in half, tends to raise 17-ketosteroid excretion and to release the pituitary gland from testicular inhibition so that it puts out its gonadotropic hormone in excessive quantities. Stilbestrol raises the estrogenic excretion rate and decreases both the androgenic excretion rate and the quantity of gonadotropic hormone in the urine. It will be remembered that on the basis of phosphatase assays also bone metastases reacted differently to castration and to stilbestrol.

On the basis of present clinical and laboratory experience, therefore, it appears best to castrate the patient suffering pain from cancer of the prostate with bone metastases because in this way pain is relieved most

promptly. Castration also can be recommended for the patient who lives at a distance and would have no regular medical supervision. I also castrate those patients who I think would discontinue estrogens on becoming comfortable. Radical perineal prostatectomy still has an important place in treating those rare individuals whose prostatic cancers have not extended beyond the bladder neck or seminal vesicles. All other patients can be treated effectively, if they respond at all to endocrine therapy, by estinyl tablets taken by mouth. Two tablets daily of .05 milligram each usually are sufficient. While this drug in this dosage is well tolerated it seems best to have it taken on retiring. I have observed no especial benefit from large doses of estrogens before relapse has occurred, nor has there appeared especial efficiency in combining both castration and estrogen administration. The estinyl tablets should not be enteric coated because it is unnecessary and it prevents one from giving an accurate dose. From one of my patients who took thirty-five enteric coated estrogen tablets, twenty-two were recovered, apparently unchanged from the stool. I have had no personal experience in performing radical perineal prostatectomy on patients who were initially inoperable but who improved after taking estrogens although Scott[17] and Coulston, urologists of great experience and skill favor the procedure. No evidence has, as yet, been produced to indicate that the old belief of "once inoperable, always inoperable" is not true.

If relapse occurs under estrogen therapy, castration should be performed. While I have never observed significant improvement from such treatments, it is possible that at least one man, Nesbit's patient, was so helped. When relapse follows castration, estinyl in doses as large as tolerated is recommended. Since with this drug larger amounts of estrogenic hormone can be given without disabling side effects, its use in this way may have promise. Clinical trial in about twenty cases of castration relapse have appeared favorable but the end results are not known. Removal of both adrenal glands to relieve these otherwise hopeless patients has, as yet, proved impracticable. In an effort to depress the output of gonadotropic hormone put out by the anterior pituitary after castration, because there is evidence that this secretion may stimulate androgen production by the adrenals, high voltage roentgen rays have been delivered to the pituitary gland. No marked or protracted benefit has been observed after treatment by us or others such as Herbst,[18] Herger and Sauer or Angrist and Khoury.

In studying the end results of five years experience in treating prostatic cancers by modification of the endocrines it is necessary to combine the reports of a number of observers because few clinics have treated sufficiently large groups of patients to have statistical significance. After treatment has been given, whether it was castration or the administration of estrogens, about 10 per cent of the men continue an uninterrupted downhill course which ends in death. The remaining patients, for the most part, are spectacularly improved. It is not possible at present to know how long this improvement will be maintained in the average case because a number of the patients treated earliest are still free from evidence of disease. However, about 65 per cent of those initially improved have since relapsed and have died. The average time that relapse occurred was thirteen months after treatment was started. The men who do not relapse within a year appear to have an excellent chance of remaining well considerably longer. While members of this more fortunate minority relapse from time to time, a small number have continued until the present in apparent good health, some with no evidence of disease. How long they can survive and whether they are truly cured is uncertain. One of our patients whose prostatic cancer was diagnosed histologically was treated with stilbestrol. He showed no evidence of tumor activity for four years when he died of coronary occlusion. An autopsy was performed and no gross or microscopic evidence of prostate tumor could be found, although sections were made of the entire prostate region. An occasional cure may therefore be possible.

Although remission of pain alone would justify the endocrine treatment of prostatic cancers the best statistics available show that the survival period of patients has been significantly prolonged as well.

TABLE III

From University of Michigan Hospital

SURVIVAL PERIOD OF 735 PATIENTS WITH PROSTATIC CANCERS BEFORE ENDOCRINE THERAPY

Average survival of entire group 21.2 months extremes 1 month and 15 years.
Average survival of 475 patients without metastases 24 months extremes 1 month and 15 years.
Average survival of 260 patients with metastases 17 months extremes 1 month and 176 months.

We are again indebted to Nesbit and his associates[1] in the University of Michigan Hospital, who, in studying their 795 patients treated without endocrine modification found that the average survival of the entire group was 21.2 months.Four hundred and seventy-five of the patients had no evidence of metastases at the time of diagnosis, and their average survival was nearly 24 months—the extremes being less than one month and 180 months (15 years). Two hundred and sixty patients had metastases at the time of diagnosis. Their average survival was 17 months —the extremes being one month and 176 months.

TABLE IV

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS NOT TREATED WITH ENDOCRINES AND THOSE CASTRATED OR GIVEN STILBESTROL

	Control 781 Cases		*Orchiectomy 75*		*Stilbestrol 50*	
Month	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	261	33.4	6	8.	1	2.
12	381	48.8	14	18.6	3	6.
18	483	61.9	22	29.3	10	20.
24	542	69.4	28	37.3	12	24.
30	568	75.	32	42.6		
36	610	78.1	41	54.4		
42	637	81.5	46	61.3		
48	648	82.9	50	66.6		

Compared with this large group are two closed series of cases under endocrine treatment which are being followed until the death of the last survivor. One series of seventy-five patients had surgical castration while the other, of fifty patients received stilbestrol by mouth. Table IV includes all patients irrespective of their condition at the time of diagnosis. It shows that the death rate for endocrine methods was much less six months after treatment was started and after forty-eight months a considerable advanage was still maintained. No comparison of the two endocrine methods seems justified because of the small numbers in the two groups.

TABLE V

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS WITHOUT METASTASES

Month	*Control 388 Cases*		*Orchiectomy 45*		*Stilbestrol 33*	
	No. Dead	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	106	27.3	2	4.4	0	0.
12	168	43.3	6	13.3	2	6.
18	211	54.3	8	17.7	4	12.1
24	233	60.0	14	31.1	5	15.1
30	255	65.7	15	33.3		
36	269	69.2	20	44.4		
42	288	72.6	23	51.1		
48	292	75.2	26	57.7		

TABLE VI

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS WITH METASTASES

Month	*Control 260 Cases*		*Orchiectomy 30*		*Stilbestrol 17*	
	No. Dead	*% Dead*	*No. Dead*	*% Dead*	*No. Dead*	*% Dead*
6	97	37.	4	13.3	0	0
12	149	57.	8	26.6	0	0
18	189	73.	12	39.9	6	35.3
24	214	82.	14	46.5	10	58.8
30	227	87.	17	56.5		
36	234	90.	22	73.1		
42	239	91.				
48	240	92.	23	76.4		

Tables V and VI also show increased longevity in patients treated by endocrine methods before and after metastasis has occurred respectively.

Even a brief review such as this shows that many investigators, studying different aspects of the problem during the past few years have added much to our knowledge of prostatic cancers and that as a

result the clinical course of many patients has been improved. Even so, only a beginning has been made. It has long been known that the clinical course of prostatic cancers depends to a great extent on their structure. Experience with endocrine therapy shows that tumor structure also strongly influences response to this form of treatment but, as yet, we are unable to correlate the two. It is also striking how uniform a pattern of end results is seen in each comprehensive group treated by modifying the endocrines but no less striking is the wide variation in the response of individual patients to the same treatment. At present knowledge does not permit individualized treatment for what must be many biologically different prostatic cancers but ignorance compels a repetition of practically the same empirical measures with each succeeding patient. With the realization of such present shortcomings it is gratifying to know that steroid hormone investigations now in progress in the laboratories of the Memorial Hospital promise to reveal clearly the one or more chemical substances which cause the origin and development of prostatic cancers. Furthermore, it is not too fanciful to predict that the time approaches when these guilty substances will be detected in young men and neutralized or destroyed before malignant changes in the prostate have begun.

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